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The risk of early cardiovascular disease in Lithuanian diabetic children and adolescents: A type 1 diabetes register database based study

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ABSTRACT

Aims: The aim was to assess the frequency and correlates of selected cardiovascular disease risk factors among Lithuanian children and adolescents with type 1 diabetes mellitus (T1DM).

Methods: A cohort of 539 T1DM children was investigated. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), glycated haemoglobin (HbA1c) was determined.

Results: The mean of HbA1c was 8.5 ± 1.8%. Overweight was present in 72 (13.4%, 95% CI 10.6–16.9) and 113 (21.0%, 95% CI 17.5–25.3) had arterial hypertension. Hypercholesterolemia was diagnosed in 120 (22.3%; 95% CI 18.6–26.7), decreased HDL in 22 (4.1%; 95% CI 2.7–6.2), high LDL in 79 (14.7%; 95% CI 11.8–18.3), and high TG in 96 (17.8%, 95% CI 14.7–21.9) subjects. There were positive linear correlations between TG and high HbA1c levels ($r = 0.192$; $p < 0.001$), and between LDL and high HbA1c levels ($r = 0.238$; $p < 0.001$). Two cardiovascular risk factors were present 14.3%, three risk factors in 6.9%, four in 2.4% and five in 0.9%. The frequency of two cardiovascular risk factors was higher among 10–17-year-old T1DM patients than among 1–9-year-old children (27.0% vs. 13.3% respectively, $p < 0.01$).

Conclusion: The frequency of cardiovascular risk factors is common in young people with T1DM and was associated with poor glycaemic control.

1. Introduction

Evidence that atherosclerosis begins early in life comes from clinical, epidemiological, and pathological studies [1,2]. Clinically, there is a familial aggregation of hypercholesterolemia and premature cardiovascular disease (CVD) [3], and a few disorders that cause hyperlipidaemia in childhood resulting in premature CVD have been described [4].

Having diabetes puts one at increased risk for cardiovascular disease (CVD) [5]. CVD is a major cause of morbidity and mortality in individuals with type 1 diabetes mellitus (T1DM) [6]. Studies have shown that these patients have a higher mortality from ischemic heart disease and higher cerebrovascular mortality at all ages compared with the general population [7,8].

Microangiopathy of the eye and kidney is the vascular disease that is seen in the majority of children with T1DM [9].

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Children with T1DM have been shown to have subclinical evidence of increased carotid intima-media thickness, reduced endothelium-dependent arterial flow-mediated dilation, and increased arterial stiffness [10,11]. Nevertheless, the atherosclerotic process in young adults with T1DM is significantly advanced compared with controls [8].

Hyperglycaemia is the primary mediator of atherosclerosis in T1DM [12]. Some studies have demonstrated serum lipid abnormalities in children and young adults with T1DM as well as an association between elevated glycated haemoglobin A1c (HbA1c) and serum lipid levels [13,14].

In 2003, an expert panel recommended that dyslipidemia in children with diabetes should be treated [15]. These recommendations were based solely on the relationship between dyslipidemia and atherosclerosis, and the panel recommended that studies regarding the relationship of glycaemic control and exercise to lipid levels are needed in both types of diabetes.

Early identification and treatment of youth at risk for early atherosclerosis requires an integrated assessment of predisposing cardiovascular disease risk factors and a comprehensive screening and treatment program [16].

The aim of our study was to determinate the prevalence and correlates of selected cardiovascular disease risk factors among Lithuanian children and adolescents with T1DM.

2. Material and methods

2.1. Subjects

The study was carried out in the department of Paediatric endocrinology of the Hospital of Lithuanian University of Health Sciences Kauno Klinikos, in the period from October 1, 2003 until September 1, 2007. All 1–17-year-old Lithuanian children and adolescents with duration of T1DM longer than 6 months were invited to participate in the study. According to the duration of T1DM patients were divided into 3 groups: 0.5–4 years (n = 309; 142 boys and 167 girls); 5–9 years (n = 158; 67 boys and 91 girls); 10–17 years (n = 71; 31 boys and 41 girls). There were only eleven T1DM patients with 15–17-year duration of disease (6 boys and 5 girls) and they were not represented as a separate group. Patients were divided into 4 groups according the age at time of investigation: $\leq$4 years (n = 13; 5 boys and 8 girls); 5–9 years (n = 85; 39 boys and 46 girls); 10–12 years (n = 111; 43 boys and 68 girls), and 13–17 years (n = 330; 153 boys and 177 girls).

2.2. Study design

The diagnosis of T1DM was made according to the WHO and DIAMOND recommended criteria [17,18]. The date of the first insulin injection was considered as the date of diagnosis.

The study protocol was approved by Bioethical committee in Kaunas University of Medicine (Nr. BE-2–33). Informed consent form 539 participants or their parents were signed.

The patients were consulted by paediatric endocrinologist, ophthalmologist, paediatric neurologist and clinical investigation, including anthropometrical measurements, evaluation of puberty, was performed. Glycaemia control and late diabetic complications, such as ophthalmic, nervous and renal function impairment, as well as dyslipidemia and other cardiovascular risk factors were evaluated.

Arterial blood pressure was measured in patients after 5 min sitting in quiet by oscillometric sphygmomanometer in sitting position in the left arm. Normal blood pressure was defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) that are <90th percentile for the gender, age, and height. Average SBP or DBP levels that were $\geq$90th percentile but <95th percentile were designated as prehypertension and were considered to be an indication of heightened risk of developing hypertension. Hypertension was defined as average SBP or DBP that was the $\geq$95th percentile for gender, age, and height on at least 3 separate occasions [19].

Height was measured using a Harpenden stadiometer (Holtain, Crymych, UK). Weight was measured using mechanical medical weights SECA 700 (SECA GMBH & CO. KG.) with precision of 0.1 kg. Body mass index (BMI) was calculated as weight (kg)/height (meters) squared [20]. BMI was evaluated according the age and gender using WHO percentile diagrams [21]. Healthy weight status was categorized in case of BMI ranging between 5th percentile to less than the 85th percentile, overweight – 85th to less than the 95th percentile and obese – equal to or greater than the 95th percentile [21].

Blood samples were collected after 14 h fast for the following parameters: HbA1c, low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol), total triglycerides (TG), total cholesterol (TC).

Measurement of HbA1c in venous blood was performed by analyser ,,Dimension Clinical Chemistry System''(DCA2000 + , Bayer Inc., USA). Optimal glycaemia control was considered when HbA1c < 7.5%, suboptimal – HbA1c 7.5–8.9%, high risk – HbA1c $\geq$9.0% [22].

TC (normal range: 3.0–5.2 mmol/l), HDL cholesterol (normal range: 1.0–2.2 mmol/l), LDL cholesterol (normal range: 1.15–3.50 mmol/l), and TG (normal range: 0.5–1.9 mmol/l) in venous blood serum samples were determined using Bayer Advia Reagent Packs and an automatic biochemical analyser (Advia, Bayer Inc., Germany).

Atherogenicity coefficient (AC) was appointed using the formula: AC = (TC–HDL cholesterol)/HDL cholesterol.

All patients received intensive insulin therapy included patients on insulin pumps as well as those on multiple daily insulin injections (>3 injections/d). The dosage was adjusted according to the results of frequent blood glucose monitoring and dietary intake. All patients received diet education according to the American Diabetes Association nutrition principles [23].

2.3. Statistical analysis

The SPSS software package was used for statistical analysis of the data (Version 14.0, Inc., Chicago, Illinois, USA) [24]. Statistical analysis was performed to compare the difference of the tested parameters between the two age groups. Mann–Whitney and Wilcoxon signed-rank tests were used for comparison [25]. Data in text, tables are means $\pm$ standard deviation (SD). A linear regression model was used to estimate trends. Multivariate logistic regression was used to estimate the odds ratios (OR) of risk factors. The 95% confidence